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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/950,022	ROTHSCHILD ET AL.
	Examiner	Art Unit
	Juliet C. Switzer	1634

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 22 September 2003.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 and 14-60 is/are pending in the application.

4a) Of the above claim(s) 1-11,14-44,47-53 and 57-60 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 45,46 and 54-56 is/are rejected.

7)☒ Claim(s) 45 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .

4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: .

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 9/22/03. Claims 10, 11, 16, 45, 46, 54, 56, have been amended, claims 12 and 13 have been canceled, and claims 59-60 have been added. Claims 1-11 and 14-60 are pending. Claims 1-9, 17-44, 47-53, and 57-58 are withdrawn from prosecution as per the original restriction requirement. In view of the amendment, claims 10, 11, 14, 15, and 16 have been withdrawn from prosecution (see below). Newly added claims 59-60 are withdrawn from prosecution as being drawn to a non-elected invention (see below). Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Election/Restrictions

1. This application contains claims drawn to an invention nonelected with traverse in the paper filed 3/19/03. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

2. Newly added claims 59 and 60 are restricted from the elected claims of group II. Furhter, claims 10, 11, 14, and 16 as amended are also drawn to a non-elected invention. The currently pending claims are grouped as follows (group numbering retained from original restriction requirement):

I. Claims 55, 59, and 60 drawn to a method of screening animals to determine whether an animal is likely to produce a larger litter when bred, classified in class 435/6.

II. Claims 45, 46, 54, 55, and 56 drawn to a method of screening animals to determine those more likely to have favorable meat quality traits, classified in class 435/6. Claim 55, which recites meat quality and litter size in the alternative is included in this group insofar as it relates to meat quality.

XI. Claims 10, 11, 14, and 16 drawn to a method of screening animals for a genotype associated with litter size and meat quality, classified in class 435/6.

This further restriction requirement is set forth in view of the amended claims. Groups II and III remain distinct from one another for the reasons set forth in the restriction requirement mailed 12/17/02 and made FINAL in the previous office action.

Groups I and IX and groups II and IX are related as a combination/subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the combination could be patentable based on the screening of animals for meat quality traits alone or based on the screening for litter size alone. The subcombinations have separate utility such as by itself, as exemplified by the fact that they are each claimed separately from the combination. Thus, in light of the amendments to the claims, amended claims 10, 11, 14, and 16 are withdrawn from proecution, and newly added claims 59 and 60 are also withdrawn as being non-elected.

Since applicant has received an action on the merits for the originally elected invention, claims 10, 11, 14, 16, 59, and 60 are now withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. The sequence listing and CRF have been received and entered.

Claim Objections

4. Claim 45 is objected to because of the following informalities:

In claim 45, line 5, the language "characterized by for" is confusing and appears to be an error. Deletion of the word "for" would obviate this concern. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 45, 46, 54, 55, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the fourth line of claim 45 the phrase "the PRKAG3 protein" does not have proper antecedent basis in the claim because the claim does not previously recite a PRKAG3 protein. The amended claim is further indefinite because it recites "favorable meat quality traits comprising color, pH level, marbling, and drip loss" but it is not clear how these are favorable traits. First of all, the claim merely sets forth that the assay is indicative of an animal possessing these traits, but all animals possess these traits, so it is not clear what the assay is determining. Further, the claims are indefinite because the idea of a "favorable" trait is entirely a relative

matter, and thus, it is unclear what is being predicted by the methods. First, the claim does not set forth what the standard of comparison is for the favorable trait. That is, the animals identified by the screen will have favorable meat quality traits compared to which other animals. Also, it is unclear what standard for improvement in meat quality traits is being applied in the instant methods, as one person's idea of an "favorable" meat quality trait may be different from another person's idea of an improved meat quality trait. Applicant is referred to the abstract provided by Lundstrom *et al.* (J. Dairy Science, Vol. 1, Suppl. 1, p. 255, abstract number 1052) who discusses meat quality traits and teaches that a phenotype that is considered within the industry as a negative trait (the RN- phenotype) is preferred by Swedish consumers but disliked by French consumers. Thus, simply to recite a method for screening for "favorable meat quality traits" is indefinite because it is unclear in whose view the good favor is to be judged, and thus, it is not clear what would constitute an favorable meat quality trait.

Claim 45 is also indefinite because the preamble of the claim recites screening animals to determine those "more likely" to have favorable meat quality traits, yet the final process step states that the particular genotypes are "indicative" of those possessing the traits, not those with an increased likelihood of possessing the traits. Thus, it is not clear which is being determined, the increased likelihood of the traits or the actual possession of the traits, as the preamble and the final process steps conflict.

Claims 46 is indefinite over the recitation "said animal having at least 95% sequence identity to SEQ ID NO: 2" because it is not clear how an animal has sequence identity to a polypeptide sequence.

In the fifth line of claim 46 the phrase "the PRKAG3 protein" does not have proper antecedent basis in the claim because the claim does not previously recite a PRKAG3 protein. Claim 46 is further indefinite over the recitation "lower level of glycogen, lactate, and glycolytic potential" because the claim does not set forth what the level is lower than, and thus it is not clear. Likewise the recitation "higher ham and loin pH" because the claim does not set forth what the level is higher than. With respect to "favorable color scores" the claim does not set forth what makes a color score "favorable." the idea of a "favorable" trait is entirely a relative matter, and thus, it is unclear what is being predicted by the methods. First, the claim does not set forth what the standard of comparison is for the favorable trait. That is, the animals identified by the screen will have favorable meat quality traits compared to which other animals. Also, it is unclear what standard for improvement in meat quality traits is being applied in the instant methods, as one person's idea of an "favorable" meat quality trait may be different from another person's idea of an improved meat quality trait. Applicant is referred to the abstract provided by Lundstrom *et al.* (J. Dairy Science, Vol. 1, Suppl. 1, p. 255, abstract number 1052) who discusses meat quality traits and teaches that a phenotype that is considered within the industry as a negative trait (the RN- phenotype) is preferred by Swedish consumers but disliked by French consumers. Thus, simply to recite a method for screening for "favorable meat quality traits" is indefinite because it is unclear in whose view the good favor is to be judged, and thus, it is not clear what would constitute an favorable meat quality trait.

In the fourth line of claim 54 the phrase "the PRKAG3 gene" does not have proper antecedent basis in the claim because the claim does not previously recite a PRKAG3 protein.

Claim 54 is also indefinite because the preamble of the claim recites screening animals to determine those "more likely" to have favorable meat quality traits, yet the final process step states that the particular genotypes are "indicative" of those possessing the traits, not those with an increased likelihood of possessing the traits. Thus, it is not clear which is being determined, the increased likelihood of the traits or the actual possession of the traits, as the preamble and the final process steps conflict. Claims 55 is also indefinite for this same reason.

In the sixth line of claim 55, the phrase "the PRKAG3 encoded gene product" does not have proper antecedent basis in the claim.

In the fourth line of claim 56, the phrase "the PRKAG3 protein" does not have proper antecedent basis in the claim.

Claim 56 is indefinite over the recitation that the "genotype" to be determined is characterized particular amino acids. The amended claim is further indefinite because it recites "favorable meat quality traits comprising color, pH level, marbling, and drip loss" but it is not clear how these are favorable traits. First of all, the claim merely sets forth that the assay is indicative of an animal possessing these traits, but all animals possess these traits, so it is not clear what the assay is determining. Further, the claims are indefinite because the idea of a "favorable" trait is entirely a relative matter, and thus, it is unclear what is being predicted by the methods. First, the claim does not set forth what the standard of comparison is for the favorable trait. That is, the animals identified by the screen will have favorable meat quality traits compared to which other animals. Also, it is unclear what standard for a favorable meat quality traits is being applied in the instant methods, as one person's idea of an "favorable" meat quality trait may be different from another person's idea of an improved meat quality trait. Applicant is

referred to the abstract provided by Lundstrom *et al.* (J. Dairy Science, Vol. 1, Suppl. 1, p. 255, abstract number 1052) who discusses meat quality traits and teaches that a phenotype that is considered within the industry as a negative trait (the RN- phenotype) is preferred by Swedish consumers but disliked by French consumers. Thus, simply to recite a method for screening for "favorable meat quality traits" is indefinite because it is unclear in whose view the good favor is to be judged, and thus, it is not clear what would constitute an favorable meat quality trait. Furthermore, the claims is indefinite because it fails to set forth in the method steps how the purpose of the claim as recited in the preamble is accomplished. That is, the claim fails to set forth how assaying for the presence of a genotype results in determining an animal more likely to have favorable meat quality traits.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 45, 46, 54, 55, and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for**...

Methods for screening pigs to determine those more likely to exhibit higher ham or loin pH, lower ham Minolta, or lower loin Minolta, comprising screening a nucleic acid sample for codons in the PRKAG3 gene that would result in the presence of an isoleucine at position 199 and an arginine at position 200 of the encoded polypeptide, wherein the presence of a genotype homozygous for isoleucine is indicative of a pig that would exhibit higher ham or loin pH and

lower ham Minolta than a pig with a different genotype at the codons encoding positions 199 and 200, and the presence of a genotype heterozygous or homozygous for isoleucine is indicative of a pig that would exhibit lower loin Minolta than a pig that does not have a nucleic acid that encodes a polypeptide with an isoleucine at position 200 of the polypeptide encoded by porcine PRKAG3. Furthermore, the specification is enabling for methods for screening pigs to determine those more likely to exhibit higher ham or loin pH, lower ham Minolta, or lower loin Minolta which comprises screening a nucleic acid sample for codons in the PRKAG3 gene that would result in the presence haplotype 3 (30T-52G-199I) as disclosed herein, wherein the presence of haplotype 3 indicates those pigs more likely to exhibit higher ham or loin pH, lower ham Minolta, or lower loin Minolta than pigs that do not have haplotype 3.

...**does not reasonably provide enablement for** methods which screen any possible animal for the same predispositions, or methods which look at genes other than the PRKAG3 gene or methods which utilize polymorphisms or haplotypes other than those specifically indicated as being supported by enabling disclosure or methods which predict an increased likelihood of any and all favorable meat quality trait. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Breadth of the Claims and Nature of the Invention

The rejected claims are drawn to methods of screening animals to determine those more likely to exhibit "favorable meat quality traits," and comprise the steps of obtaining biological

samples from animals and assaying for the presence of particular genotypes associated with improved meat quality traits.

Claim 45 recites a method of screening animals which comprises assaying the PRKAG3 protein in a sample for the threonine at amino position 30, a glycine at amino acid postion 52 and an isoleucine at amino acid position 199 in SEQ ID NO: 2 "or an equivalent position to SEQ ID NO: 2" when two proteins are aligned. Claim 45 encompasses methods which predict the presence of any meat quality trait in any animal as the broad language "comprising" encompasses the recited traits but any other traits as well.

Claim 46 is drawn to a method of screening animals to determine those more likely to have favorable meat quality traits which comprises assaying for the presence of a genotype characterized by isoleucine at position 199 and arginine at position 200 in SEQ ID NO: 2 or an equivalent position in SEQ ID NO: 2. The final clause of claim 46 recites that the presence of the isoleucine and agrinine are indicative of an animal having lower level of glycogen, lactate and glycolytic potential, higher ham and loin pH and favorable color scores

Claim 54 is drawn to a method for screening animals to determine those more likely to have favorable meat quality traits comprising assaying for the presence of a genotype characterized by a combination of at least two polymorphisms in the PRKAG3 gene. Claim 54 encompasses methods which predict the presence of any meat quality trait in any animal, utilizing any possible polymorphism within the PRKAG3 gene that is associated with meat quality traits.

Claim 55 is drawn to a method for screening animals to determine those more likely to have favorable meat quality traits comprising assaying for the presence of a genotype

characterized by the a combination of at least two polymorphisms in the PRKAG3 gene. Claim 55 encompasses methods which predict the presence of any meat quality trait in any animal, utilizing any possible polymorphism within the PRKAG3 gene that is associated with meat quality traits. Claim 55 also recites methods of predicting increased value for litter size, but these methods are non-elected.

Claim 56 recites a method of screening animals which comprises assaying for the presence of a genotype that results in threonine at amino acid position 30, a glycine at amino acid 52, and an valine at amino acid 199. Claim 56 encompasses methods which predict the presence of any meat quality trait in any animal, and via the detection of the amino acids within SEQ ID NO: 2 or "an equivalent position" of any other polypeptide.

The nature of the invention is that it relies on analysis of biological samples for the detection of particular alleles at present at polymorphic sites. Based on the presence or absence of particular alleles, one can presumably make assumptions about the likelihood of the presence or absence of meat quality traits. The invention sets forth a screen for animals possessing "favorable" meat quality traits, but does not set forth in whose eyes the improvement is to be measured. Meat quality is largely a matter of relative opinion, with some individuals preferring meat with particular traits and others preferring different traits. Thus, the judgment of an "favorable" meat quality is largely subjective. For example, Lundstrom *et al.* discusses meat quality traits and teaches that a phenotype that is considered within the industry as a negative trait (the RN- phenotype) is preferred by Swedish consumers but disliked by French consumers. The invention encompasses the prediction of meat quality traits in any animal for which this might be of interest, and since a wide variety of animals are raised for meat production

(including, for example, pigs, sheep, cows, buffalo, chickens, turkeys, geese, game hens, frogs, fish of all kinds, sharks), the scope of these claims is quite broad with respect to animal type encompassed.

Direction Provided and Working Examples

The specification teaches that "favorable meat quality trait" means a significant improvement in one of many measurable meat quality traits above a given population (p. 6). The specification further provides that examples of such traits include, but are not limited to, loin Minolta lightness, loin Japanese color score, loin marbling, loin pH, ham minolta lightness, ham pHu and drip loss or purge (p. 6-7). Other quality traits include meat juiciness and tenderness in sensory tests, percentage of fat in the meat, and meat texture measures.

Applicants provide examples which teach the analysis of an intercross between Berkshire and Yorkshire (BxY) pig breeds yielding 525 F_2 offspring, some F3 offspring, and the analysis of blood samples from a large collection of five different commercial lines of pigs (p. 38). Applicants removed from their analysis any samples that had a Q at position 200 of the encoded polypeptide, thus all samples examined in applicant's analysis had the R200 genotype (p. 39). Within the founders of the BxY family and some F_3 individuals, applicants identified three missense mutations, at positions 30, 52, and 199 of the PRKAG3 polypeptide (p. 42). Applicants teach a novel missense mutation with the porcine PRKAG3 gene which results in a G52S substitution in the encoded polypeptide (p. 42).

Applicants completed a F_2 association study and found that all three of the missense mutations had significant effects on average glycogen and lactate content and on glycolytic potential (p. 43). Applicants further teach that for pigs, the most significant effects were

revealed for the I199V polymorphism for the traits analyzed, including glycogen and lactate content and glycolytic potential measures, and also in some of the meat quality traits associated with these measures (p. 43). For example, pigs that were homozygous for the codon encoding isoleucine at position 199 had significantly higher ham pH and loin pH (Table 4, page 59). However, pigs that were heterozygous for the codon encoding isoleucine at position 199 did not display significantly different pH than pigs homozygous for the codon encoding valine at position 199. This is true for ham Minolta L and ham Minolta b as well. Only for the loin Minolta measures did the presence of a single codon encoding isoleucine predict a significant difference between the groups. Applicants teach that for five lines of commercial pig breads, across all breeds, I199V is kept in the model for six tested meat quality traits, G52S for ham pH, loin pH, loin Minolta L, and ham Minolta b, and T30N was kept in the model for ham Minolta L, loin Minolta L and ham Minolta b (p. 43). The specification teaches that across and within line analyses showed haplotype 3 (30T-52G-199I) as having the highest effect which was significantly different from each other haplotypes for ham pH. The specification does not disclose any other significant relationships between meat quality traits and haplotypes, thus, methods for determining improved meat quality by assaying for the presence of haplotype 2 (as in claim 56) are not enabled by the instant specification.

With regard to the application of the methods taught in the instant specification to animals other than pigs, the specification merely asserts that "it is expected that the different alleles disclosed herein will also correlate with variability in this gene in other economic or meat-producing animals such as bovine, sheep, chicken, etc." The specification is silent with respect to the nucleotide or amino acid sequence of the PRKAG3 gene or encoded polypeptide

from other such species of meat producing animals, and the specification does not provide any evidence that the polymorphisms disclosed herein are present in other animal species or that even if the polymorphisms are present that they are also indicative of any particular meat quality traits.

State of the Art, Level of skill in the Art, and Level of Unpredictability in the Art

The prior art teaches the RN- phenotype in pigs, which is associated with high glycogen content in Hampshire pig skeletal muscles (for example, Milan *et al.* 2000, and references cited therein). This phenotype is considered technically to have large effects on meat quality and processing, pigs meat from having the phenotype has low ultimate pH, reduced water-holding capacity and a reduced yield of cooked ham, however the mutation is considered to have beneficial effects on meat content (ABSTRACT, Milan *et al.*). Milan *et al.* isolated the porcine PRKAG3 gene and a identified human version of the gene. Milan *et al.* screened the entire coding region of the porcine PRKAG3 gene for polymorphisms, and identified five PRKAG3 polymorphic sites within the positions of the PRKAG3 gene that code for codons 30, 53, 193, 194, 199, 200, and 372 of the porcine PRKAG3 polypeptide (Table 1). Milan *et al.* teach that only the R200Q allele was exclusively associated with RN-, with the "Q" version being present in the RN- pigs. The "Q" allele was found only in RN- Hampshire pigs, and neither the "Q" allele nor the RN- phenotype were observed in other breeds of pigs (Milan *et al.* p. 1249). Milan *et al.* also teach that with the in the RN- pigs a "V" is present at position 199 and an "I" is present in all rn+ pigs.

The prior art does not provide the nucleotide or amino acid sequences of other meat species, nor does the prior art provide any additional polymorphisms within the porcine PRKAG3 gene that are associated with meat quality traits.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with particular phenotypes. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a physiological state or physical trait. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma ($p=0.294$). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the PRKAG3 gene, and in some cases shown that they are reliable markers of some meat traits, it remains highly unpredictable that any of these polymorphisms exist in other species of animals, and even if they do exist, that they are indicative of any particular phenotypic trait. Vincek *et al.* (Mammalian Genome 5, 376-379 (1994)) demonstrate that polymorphisms that are present in the beta globin region in human were not able to be located in chimpanzee and gorilla. Thus, simply because a particular polymorphism is present in one species of animal, there is no evidence that it will be present in another animal.

The ability to apply the assays disclosed in the instant specification to a wide range of animals relies on an assumption of a structure/function correlation across different species of animals, however, no evidence of such a relationship has been provided in the specification. The application of the instantly disclosed assay to additional species of animals requires one to assume that these particular polymorphisms will be present at “equivalent positions” in other animals, however, applicant has not disclosed the importance of these polymorphisms for the function of the PRKAG3 gene or encoded polypeptide, and so it is difficult if not impossible to determine the equivalent positions in the undisclosed PRKAG3 genes of other animals. Applicant has not provided any guidance as to how to determine which amino acid position in the other species of animals would be the “equivalent” positions to amino acids 199 and 200 of the porcine PRKAG3 encoded polypeptide. The specification and claim 10 refer to using BLAST to make such a determination, but fail to clearly define what in fact makes the position

and "equivalent"—for example, are only positions that are 199 and 200 in the homologues of other animals the equivalent, regardless of surrounding amino acids? Is a certain percentage of homology or a run of common amino acids required to determine the equivalent? Is the equivalent position based on the three dimensional structure of the encoded polypeptide, such that the equivalent polymorphic position would have to be in a similar morphological position in the encoded polypeptide? No guidance is provided in the specification to further guide the practitioner to the "equivalent" positions, and such a determination is highly unpredictable.

The prior art does not provide the sequence of the PRKAG3 gene in other meat producing animal species, and neither does the instant specification. Due to this lack of critical information about the sequence of the PRKAG3 gene in other animal species, at the time the invention was made it was not possible to even predict what the equivalent positions of the polymorphisms disclosed herein would be in other animals. Further, it is not even clear that the PRKAG3 gene in other species of meat producing animals would have the same effects on meat quality as the PRKAG3 gene in pigs. Juppner (Bone Vol. 17, No. 2, Supplement, August 1995: 39S-42S) teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (ABSTRACT and p. 39S-40S). Thus, even if homologues of PRKAG3 gene were identified and sequenced in other animals, and even if these displayed polymorphisms, it is highly unpredictable as to whether these putative polymorphisms would be indicative of any particular meat traits in the animals.

Quantity of Experimentation

An extensive, and prohibitive amount of experimentation would be required to practice this invention commensurate with the full scope of these claims. Applicants have disclosed that

two generations of animals were bred and screened and a large collection of blood samples for five different lines commercial pigs were collected and screened in order to establish relationships between the instantly disclosed polymorphisms and meat quality traits. Because there is no reason to expect that the instantly disclosed polymorphisms would exist in species of animals other than pigs, or that other polymorphisms exist within the PRKAG3 gene that are indicative of meat quality traits, screening for additional polymorphisms in pigs or other animal species would require breeding and screening hundreds of thousands of animals. There is no evidence, however, of any frequency of significant polymorphisms in other meat producing animals, a genus which encompasses fowl, mammals, and indeed, even some reptiles. Further, as noted above, even in positive matches, the PRKAG3 polymorphism may not correlate with meat quality traits, since such a correlation is highly unpredictable.

Thus, in light of the broad nature of the claims, the lack of examples and guidance in the specification beyond the teachings of polymorphisms in pigs associated with particular traits, the high level of unpredictability in the prior art, and the high quantity of experimentation necessary to practice the claimed invention commensurate with its full scope, it is concluded that undue experimentation would be necessary to practice the claimed invention commensurate with its full scope.

Priority

9. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 45, 46, 54, 55, and 56 of this application. This application claims priority to three provisional applications. None of these provide adequate

support under 112 1st paragraph for the claims to their full scope for at least the same reasons why the instant specification does not provide adequate support for the claims. Furthermore, none of the provisional applications provides support for the methods which examine particular haplotypes since these provisional applications do not provide analysis of the relationship between meat quality traits and any particular haplotypes. Thus, the filing date for the elected claims is considered to be the instant filing date, 9/10/01.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 45, 46, 54, and 55 are rejected under 35 U.S.C. 102(a) or 102(b) as being anticipated by Milan *et al.* (Science, 19 May 2000, Vol. 288, pages 1248-1251). Milan *et al.* teach a method for screening animals to determine those more likely to exhibit improved meat quality traits comprising:

obtaining a biological sample of material from said animal (p. 1249);

and

assaying for the presence of a genotype characterized by a polymorphism in the PRKAG3 gene characterized by an amino acid of valine at position 199 and an amino acid of arginine at position 200 (Table 1, alleles 2-4) OR an isoleucine at position 199 and an arginine at position 200 (Table 1, allele 5)

Specifically, Milan *et al.* teach that animals with their alleles 2-5 have higher meat quality (as indicated by their having the rn+ allele) than animals that have allele 1 as designated by them. Milan *et al.* determine nucleotide sequence of the PRKAG3 coding sequence by RT-PCR analysis, and thus they amplify the section of the PRKAG3 gene that contains the polymorphism, including the region that contains the BsaHI site. This rejection applies to claim 12 insofar as sequencing the gene can be considered one method of testing for short interspersed elements. This rejection applies to claims 13 and 16 insofar as it is unclear what primers are required to meet the limitations of the claims, but so far as Milan *et al.* do perform amplification prior to detection of the polymorphisms.

Furthermore, Milan *et al.* teach a method wherein they detect a threonine at amino acid position 30, a glycine at amino acid 52 and an isoleucine at amino acid position 199. Such a detection takes place in their allele 5 which is an allele from rn+ pigs. In all of the alleles detected by Milan *et al.*, a glycine was encoded at amino acid 52 (see Fig. 2), and thus the detection of such a nucleic acid encoding the amino acids recited in claim 45 is inherent in the methods taught by Milan *et al.*

Response to Remarks

With regard to the comments about "improved" meat quality traits (reiterated herein with regard to "favorable" meat quality traits) applicant's insertion of particular traits into the claims does not elimiate the fact that this phraseology is relative. There is no standard given in the claims. The specification states that a "favorable" trait means a significant improvement in one of many measurable meat quality traits above a given population, but the claims do not give the population for comparison, and therefore remain relative with no standard for comparison.

New 112 2nd rejections have been set forth to address the amended claims.

With respect to the scope of enablement rejection, applicants submit that due to the highly conserved nature of the protein it is expected that other animals will demonstrate polymorphisms in this protein which can be determined by sequence homology or other similar effects. First, the prior art does not provide the nucleotide or amino acid sequences of other meat species, and thus the statement that this is a "highly conserved" protein is unsupported with regard to any species of animal whose meat quality would be of interest. Further, the identity and location and effects of these polymorphisms remains unknown and highly unpredictable as discussed in the rejection of record. The rejection is maintained.

With respect to the claim about priority, applicant's comments are acknowledged, however, they are not persuasive as the priority documents do not support the full scope of the claims for at least the reasons discussed in the 112 1st paragraph rejection. With regard to the comments about haplotypes in serial number 60/299111, it is noted that this section teaches that the 199V-200R polymorphism combination is associated with increased glycogen and decreased pH compared with 199I-200R haplotype. The priority documents, at the very least, do not provide support for claims which encompass the screening of animals other than pigs or claims which comprise the screening for polymorphisms other than those disclosed herein. Thus, the denial of priority is maintained.

Applicants argue that Milan *et al.* does not anticipate the instantly claimed invention. Applicants argue that Milan *et al.* merely disclose the sequence of the PRKAG3 and some polymorphisms for the gene indicating that the mutation at position 200 is causative for a major effect known as RN-. However, as noted in the rejection, the teachings of Milan *et al.* meet all

of the structural limitations of the instantly rejected claims, that is, the provide the practice of all of the required method steps, and thus they meet the methods of the claims, and the rejection is maintained.

The declaration filed by Rothschild is not persuasive to overcome the Milan *et al.* reference because the effective filing date of the application is considered 9/10/01, and thus, at this time Rothschild *et al.* has a publication date that is more than a year from the filing date, and thus though the reference is applied under both 102(a) and (b) the reference cannot be sworn behind because at this time it is a statutory bar. If further prosecution of this application leads to a granting of priority to a provisional application or application(s) then the merits of the declaration will be reconsidered at that time for the purposes of determining that the declaration properly antedates the reference.

MPEP 2132.01 states:

> When the reference is not a statutory bar under 35 U.S.C. 102(b), (c), or (d), applicant can overcome the rejection by swearing back of the reference through the submission of an affidavit under 37 CFR 1.131. In re Foster, 343 F.2d 980, 145 USPQ 166 (CCPA 1965). If the reference is disclosing applicant's own work as derived from him or her, applicant may submit either a 37 CFR 1.131 affidavit to antedate the reference or a 37CFR 1.132 affidavit to show derivation of the reference subject matter from applicant and invention by applicant. In re Facius, 408 F.2d 1396, 161 USPQ 294 (CCPA 1969). See MPEP § 715 for more information on when an affidavit under 37 CFR 1.131 can be used to overcome a reference and what evidence is required.

Conclusion

12. A method which detects a nucleic acid encoding a serine at position 52 of the amino acid sequence of the porcine PRKAG3 gene as depicted in instant SEQ ID NO: 2 has not previously been disclosed in the prior art.

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM. Please note that beginning January 13, 2003 the examiner's telephone number will change to (571) 272-0753.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (703) 308-1119. Beginning January 13, 2003 Gary Benzion's telephone number will change to (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JSwitzer

Juliet C Switzer
Examiner
Art Unit 1634

December 15, 2003

Gary Benzion

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